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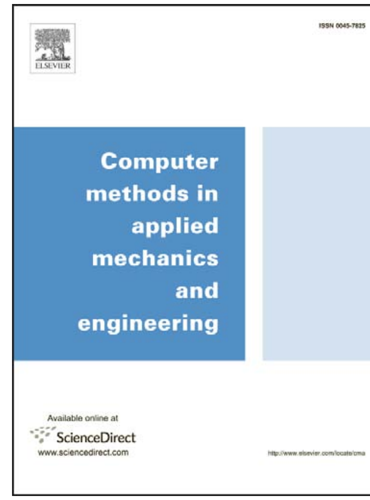

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Coupled vehicle-skin models for drug release *

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Abstract

Percutaneous absorption of a drug delivered by a vehicle source is usually modeled by using diffusion Fick's law. In this case, the model consists in a system of partial differential equations of diffusion type with a compatibility condition on the transition boundary between the vehicle and the skin. Using this model, the fractional drug release in both components - vehicle and skin - is proportional to the square root of the release time. Often experimental results show that the predicted drug concentration distribution in the vehicle and in the skin by the Fick's model does not agree with experimental data. In this paper we present a non-Fickian mathematical model for the introduced percutaneous absorption problem. In this new model the Fick's law for the flux is modified by introducing a non-Fickian contribution defined with a relaxation parameter related to the properties of the components. Combining the flux equation with the mass conservation law, a system of integro-differential equations is established with a compatibility condition on the boundary between the two components of the physical model. The stability analysis is presented. In order to simulate the mathematical model, its discrete version is introduced. The stability and convergence properties of the discrete system are studied. Numerical experiments are also included.

1 Introduction

Percutaneous drug delivery is the penetration of drugs from an outside source - the vehicle - through the skin passing the viable epidermis into the blood capillaries and the lymphatic system. The delivery device is a polymeric system which can be a hydrophilic polymer, a hydrogel or another polymeric matrix containing the drug. The polymeric matrix plays the major role as it should keep the drug available on the skin surface with a constant concentration over a long time period. In monolithic systems, the transdermal system has three different layers, an impermeable backing, an intermediate polymer matrix containing the drug and a skin adhesive layer. The polymeric matrix is designed to control the drug diffusion through the system to the skin ([32]).

Let us consider the vehicle-skin system represented in Figure 1. The objective is to calculate the concentration of the drug, in the vehicle and in the skin, at time t in the transversal sections $T(x')$ and $T(x'')$, respectively, which are parallel to the yoz plane.

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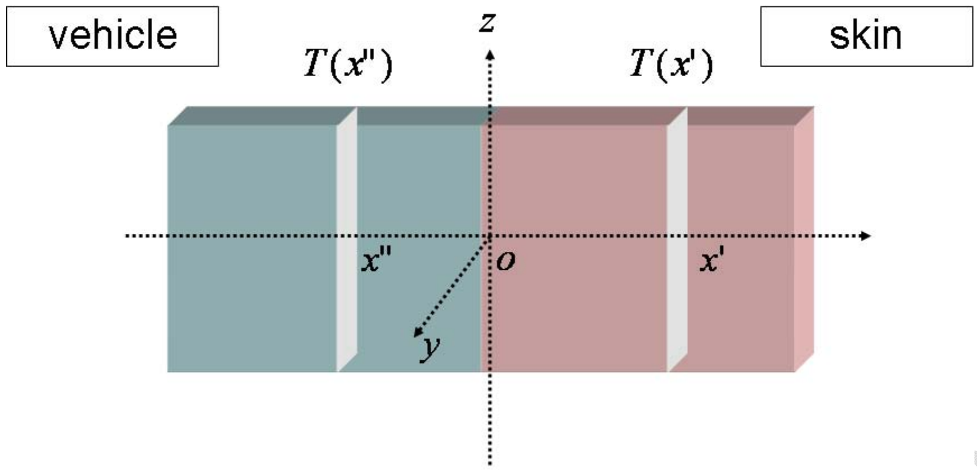


Figure 1: The vehicle-skin system

Assuming that both system components are homogeneous the vehicle-skin system presented in Figure 1 can be modeled as a one-dimensional system. Then our problem consists of the computation of the drug concentration $c(x,t)$ at spatial point x and at time $t \geq 0$ for $x \in [-L_v, L_s]$, where L_v and L_s are the vehicle and the skin lengths and the origin is the transition point. We assume that the left boundary of the vehicle is isolated and the boundary of the skin in contact with the right boundary of the vehicle does not offer any resistance to the drug passage. This means that the drug that arrives to the right boundary of the vehicle passes to the skin. The drug concentration that passes to the blood is proportional to the drug concentration at the right boundary of the skin.

Traditionally the introduced diffusion problem is modeled by the classical diffusion equation

$$\frac{\partial c}{\partial t}(x,t) = D_i \frac{\partial^2 c}{\partial x^2}(x,t), x \in I_i, t > 0, \tag{1}$$

with $i = v$ when $x \in I_v = (-L_v, 0)$ and $i = s$ when $x \in I_s = (0, L_s)$. As the left boundary of the vehicle is isolated, the flux at $x = -L_v$ is null which implies for the drug concentration at this point the next condition

$$\frac{\partial c}{\partial x}(-L_v, t) = 0, \, t > 0. \tag{2}$$

In the physical model it was assumed that the drug concentration that passes to the blood at $x = L_s$ is proportional to the drug concentration at this point which means that

$$\frac{\partial c}{\partial x}(L_s, t) = -rc(L_s, t), t > 0, \tag{3}$$

where r is a positive constant.

Furthermore, as the drug flux that arrives to the right boundary of the vehicles passes to the skin, for the drug concentration at $x = 0$ we have

$$D_v \frac{\partial c}{\partial x}(0,t) = D_s \frac{\partial c}{\partial x}(0,t), t > 0. \tag{4}$$

Finally we can assume that

$$c(x, 0) = c_0(x), x \in (-L_v, L_s), \tag{5}$$

because the initial drug distribution is known.

The classical diffusion model (1) - (5) was considered for instance in [20], [28], [38], [39]. This model is established by using the Fick's law for the flux $J_i(x,t)$ at point x at time t, which states that

$$J_i(x,t) = -D_i \frac{\partial c}{\partial x}(x,t), \tag{6}$$

with $i = v$ if $x \in I_v = (-L_v, 0)$ and $i = s$ if $x \in I_s = (0, L_s)$, where $D_i > 0$, for $i = v, s$, represents the diffusion coefficient in the vehicle and skin media respectively.

The solution of the classical diffusion equation (1) has the unphysical property that if a sudden change in the concentration is made at a point in the polymer or in the skin, it will be felt instantly everywhere. This property, known as infinite propagation speed, is not present in drug conduction phenomena and it is a consequence of the violation of principle of casuality by the Fick's law (6) for the flux. This problem was also observed in heat conduction problems in mathematical models based on the Fourier law for heat flux for instance in [8], [29], [40]. For reaction-diffusion systems the same drawback was observed in [18], [19].

The Fick's law for the flux is based on Brownian motion in fluid systems. The assumptions of the Brownian motion are not compatible with biological barriers such as the human skin. In fact the transport of substances across this membrane is a complex phenomenon comprising physical, chemical and biological interactions. It is evident from the published results that Fick's law often does not offer a good approximation to dermal absorption (see e.g. [1], [27], [30]). The concentration profiles obtained with the classical diffusion model do not agree with experimental results. A delay effect appears in this data.

It should be also pointed out that the movement of the drug particles in the polymeric device is not of Brownian type since the particle flux is not well described by Fick's law. For instance, the structure of the polymer chains of hydrogel based devices can change in contact with water or can depend on the pH and on the ionic strength of the surrounding environment. At the same time the drug trapped inside of the hydrogel starts to diffuse out of the network. Often the transport mechanism in this type of systems does not behave according to Fickian diffusion. In fact, the results obtained in experimental context support the previous sentence ([6], [10], [25], [31], [33], [34], [36], [37], see also [35] and the references contained in the last paper). However, often we find in the literature mathematical models for percutaneous drug absorption considering the system vehicle-skin established by using Fick's law (see e.g. [20], [22], [23], [28]).

Let us consider that the flux J_i has two main contributions: one of the Fickian type,

$$J_{i,F}(x,t) = -D_{1,i} \frac{\partial c}{\partial x}(x,t),$$

and another, $-J_{i,M}(x,t)$, taking into account the memory effect of the diffusion phenomena. This means that $J_i(x,t) = J_{i,F}(x,t) + J_{i,M}(x,t)$.

The flux $J_{i,M}$ at point x and at time t is considered as being a consequence of the concentration variation at point x and at some passed time,

$$J_{i,M}(x,t) = -D_{2,i} \frac{\partial c}{\partial x}(x, t - \tau_i),$$

where $i = v, s$, τ_v and τ_s are the relaxation time associated with the vehicle and with the skin, respectively. The relaxation parameters represent the time needed for one part of the media - vehicle, skin - to change in neighboring parts. We assume that the delay parameters are very small.

Taking a first order approximation to the flux and integrating the first order differential equation, we obtain

$$\frac{\partial J_{i,M}}{\partial t}(x,t) + \frac{1}{\tau_i} J_{i,M}(x,t) = -\frac{D_{2,i}}{\tau_i}\frac{\partial c}{\partial x}(x,t)$$

with

$$J_{i,M}(x,t) = -\frac{D_{2,i}}{\tau_i}\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(x,s)\,ds. \tag{7}$$

Note that, when $\tau_i \to 0$, the flux $J_i(x,t)$ defined by (7) tends to the classical Fick's flux. The previous deduction can be avoided defining the new flux by (7). In fact we can argue that the flux is not proportional to the gradient of the drug concentration but it is proportional to the "average in time" of the gradient of the concentration.

Considering the mass conservation law

$$\frac{\partial c}{\partial t}(x,t) = -\frac{\partial J_i}{\partial x}(x,t)$$

we obtain for the drug concentration the following integro-differential equations

$$\frac{\partial c}{\partial t}(x,t) = D_{1,i}\frac{\partial^2 c}{\partial x^2}(x,t) + \frac{D_{2,i}}{\tau_i}\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial^2 c}{\partial x^2}(x,s)\,ds,\ x\in I_i, t>0, \tag{8}$$

with $i = v$ when $x \in I_v = (-L_v, 0)$ and $i = s$ when $x \in I_s = (0, L_s)$.

Considering now the flux definition, the boundary conditions are rewritten in the following form

$$D_{1,v}\frac{\partial c}{\partial x}(-L_v,t) + \frac{D_{2,v}}{\tau_v}\int_0^t e^{-\frac{t-s}{\tau_v}}\frac{\partial c}{\partial x}(-L_v,s)\,ds = 0, \tag{9}$$

$$D_{1,s}\frac{\partial c}{\partial x}(L_s,t) + \frac{D_{2,s}}{\tau_s}\int_0^t e^{-\frac{t-s}{\tau_s}}\frac{\partial c}{\partial x}(L_s,s)\,ds + rc(L_s,t) = 0, \tag{10}$$

The integro-differential equations for the vehicle-skin system are complemented with the initial drug distribution (5) and with the transition condition at $x = 0$ defined now by

$$D_{1,v}\frac{\partial c}{\partial x}(0,t) + \frac{D_{2,v}}{\tau_v}\int_0^t e^{-\frac{t-s}{\tau_v}}\frac{\partial c}{\partial x}(0,s)\,ds = D_{1,s}\frac{\partial c}{\partial x}(0,t) + \frac{D_{2,s}}{\tau_s}\int_0^t e^{-\frac{t-s}{\tau_s}}\frac{\partial c}{\partial x}(0,s)\,ds, \tag{11}$$

$t > 0$.

The boundary conditions (9), (10) and the transition condition (11) are the natural conditions associated with the integro-differential model, as it will be explained in the next section.

Equation (8) can also be obtained if we assume that the vehicle and the skin have a viscoelastic response to the sudden strain induced by the penetration of the drug. In this case the flux $J_{i,M}$ is related with the viscoelastic stress σ_i by

$$J_{i,M}(x,t) = D_{2,i}\frac{\partial \sigma_i}{\partial x}(x,t),$$

and

$$\frac{\partial \sigma_i}{\partial t}(x,t) + \frac{1}{\tau_i}\sigma_i = c(x,t). \tag{12}$$

The definition (12) for the viscoelastic stress σ_i is a particular case of the definition given by Cohen, White and Witelski in [9], where on the second member of (12) a linear combination of

$c(x,t)$ and $\dfrac{\partial c}{\partial t}(x,t)$ was considered. The approach introduced in [9] was largely followed in the literature. Without being exhaustive we mention [11]- [17], [24].

In heat conduction phenomena equation (8) was used in [8], [29] and [40] in order to avoid the limitation of the traditional heat equation. In reaction-diffusion context equation (8) with a reaction term was introduced in [18], [19] in order to avoid the drawback of the classical Fisher-Kolmogorov-Petrovskii-Piskunov equation. Equation (8) was studied in [2], [3], [4] and [21] being used to model the drug diffusion in the skin in [5].

In this paper, our aim is to study analytically and numerically the initial boundary value problem (IBVP) (8)-(11). From an analytical view point, Section 2 focuses on the stability of the mathematical model. In Section 3 a discrete version of the continuous model is proposed and its stability and convergence properties are analyzed. Finally, in Section 4 we present some numerical simulations to illustrate the theoretical results. The behavior of the Fickian model and the non-Fickian model is compared numerically.

2 On the well-posedness of the non-Fickian model

In this section we analyse the stability of the IBVP (8)-(11) with respect to perturbations of the initial condition.

We use the following notation: by $v(t)$ we denote the x-function if v is defined in $[-L_v, L_s] \times [0,T]$ and t is fixed. We represent by $(.,.)$ the usual L^2 inner product and by $\|.\|$ the usual L^2-norm. When we consider each interval $I_i, i = v, s$, we adopt the following notations: $(.,.)_{I_i}$, $\|.\|_{L^2(I_i)}$. By $H^1(-L_v, L_s)$ we represent the usual Sobolev space. Let $L^2(0,T,H^1(-L_v,L_s))$ be the space of functions v defined in $[-L_v,L_s]\times[0,T]$ such that, for $t \in [0,T]$, $v(t) \in H^1(-L_v,L_s)$ and

$$\int_0^T \|v(t)\|_1^2\, dt < \infty,$$

where $\|.\|_1$ denotes the usual norm in $H^1(-L_v,L_s)$. Let $L^2(0,T,L^2(-L_v,L_s))$ be defined as $L^2(0,T,H^1(-L_v,L_s))$ replacing $H^1(-L_v,L_s)$ by $L^2(-L_v,L_s)$.

We establish, in the following result, an estimate for the energy functional

$$E(t) = \|c(t)\|^2 + \sum_{i=v,s}\Big(D_{1,i}\int_0^t \|\frac{\partial c}{\partial x}(s)\|^2_{L^2(I_i)}\, ds + \frac{D_{2,i}}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\, ds\|^2_{L^2(I_i)}\Big)$$

for $t \in [0,T]$, depending on the behavior of the initial condition $c_0(x,t)$ for $x \in [-L_v, L_s]$.

Theorem 1 *Let c be a solution of (8)-(11) such that $c \in L^2(0,T,H^1(-L_v,L_s))$ and $\dfrac{\partial c}{\partial t}, \dfrac{\partial^2 c}{\partial x^2} \in L^2(-L_v,L_s)$, for each $t \in (0,T]$. Then we have*

$$E(t) \leq \|c_0\|^2,\ t \in [0,T]. \tag{13}$$

Proof: Multiplying (8) by $c(t)$ with respect to the inner product $(.,.)$ and using integration by parts we get

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|c(t)\|^2 &= -\sum_{i=v,s}\Big(D_{1,i}\|\frac{\partial c}{\partial x}(t)\|^2_{L^2(I_i)} + \frac{D_{2,i}}{\tau_i}(\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds, \frac{\partial c}{\partial x}(t))_{I_i}\Big)\\
&\quad -c(-L_v,t)\Big(D_{1,v}\frac{\partial c}{\partial x}(-L_v,t) + \frac{D_{2,v}}{\tau_v}\int_0^t e^{-\frac{t-s}{\tau_v}}\frac{\partial c}{\partial x}(-L_v,s)\,ds\Big)\\
&\quad +c(0,t)\Big(D_{1,v}\frac{\partial c}{\partial x}(0,t) + \frac{D_{2,v}}{\tau_v}\int_0^t e^{-\frac{t-s}{\tau_v}}\frac{\partial c}{\partial x}(0,s)\,ds\\
&\quad -c(0,t)\Big(D_{1,s}\frac{\partial c}{\partial x}(0,t) + \frac{D_{2,s}}{\tau_s}\int_0^t e^{-\frac{t-s}{\tau_s}}\frac{\partial c}{\partial x}(0,s)\,ds\Big)\\
&\quad +c(L_s,t)\Big(D_{1,s}\frac{\partial c}{\partial x}(L_s,t) + \frac{D_{2,s}}{\tau_s}\int_0^t e^{-\frac{t-s}{\tau_s}}\frac{\partial c}{\partial x}(L_s,s)\,ds\Big).
\end{aligned}$$

Taking into account the boundary conditions (9), (10) and the transition condition (11) we establish

$$\begin{aligned}
\frac{1}{2}\frac{d}{dt}\|c(t)\|^2 &= -\sum_{i=v,s}\Big(D_{1,i}\|\frac{\partial c}{\partial x}(t)\|^2_{L^2(I_i)} + \frac{D_{2,i}}{\tau_i}(\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds, \frac{\partial c}{\partial x}(t))_{I_i}\Big)\\
&\quad -rc(L_s,t)^2. \qquad (14)
\end{aligned}$$

As we have

$$\begin{aligned}
(\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds, \frac{\partial c}{\partial x}(t))_{I_i} &= \frac{1}{2}\frac{d}{dt}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}\\
&\quad +\frac{1}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)},
\end{aligned}$$

we deduce that

$$\frac{d}{dt}E(t) = -\sum_{i=v,s}\Big(D_{1,i}\|\frac{\partial c}{\partial x}(t)\|^2_{L^2(I_i)} + \frac{2}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}\Big) - 2rc(L_s,t)^2$$

and we conclude (13).

■

The designation "natural conditions" for the boundary conditions (9), (10) and the transition condition (11) is justified in the proof of Theorem 1. In fact such conditions enable us to conclude that the total mass in the vehicle and in the skin is bounded in time. The same behavior can be observed for the gradient of the concentration in both components of the vehicle-skin system as well as for the weighed "past in time" of the concentration gradients $\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}$, $i = v, s$. Furthermore, from the proof of Theorem 1 we conclude that $E(t)$ is decreasing in time.

We point out that for the Fickian model (1) - (5) we are not able to get any information to the weighed "past in time" of the concentration gradients $\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}$, $i = v, s$.

If the boundary conditions (9)-(10) are replaced by the homogeneous Dirichlet boundary conditions, then using the Poincaré-Friedrichs inequality in both terms $D_{1,i}\|\frac{\partial c}{\partial x}(t)\|^2_{L^2(I_i)}$ we obtain

$$\begin{aligned}&\frac{d}{dt}\Big(\|c(t)\|^2+\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}\Big)\\ &\leq \mathcal{C}\Big(\|c(t)\|^2+\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}\Big)\end{aligned} \tag{15}$$

with

$$\mathcal{C}=\max\{-\frac{2D_{1,v}}{L_v^2},-\frac{2D_{1,s}}{L_s^2},-\frac{2}{\tau_v},-\frac{2}{\tau_s}\}.$$

From (15) we deduce that

$$\|c(t)\|^2+\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}\leq e^{\mathcal{C}t}\|c_0\|^2, t\geq 0, \tag{16}$$

which allow us to conclude, in this case, that

$$\lim_{t\to\infty}\Big(\|c(t)\|^2+\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\int_0^t e^{-\frac{t-s}{\tau_i}}\frac{\partial c}{\partial x}(s)\,ds\|^2_{L^2(I_i)}\Big)=0.$$

Estimate (16) characterizes the drug mass in the vehicle and in the skin at each time t as well as the weighed "past in time" of the concentration gradients. Such characterization can not be obtained for the Fickian model (1) - (5) even if homogeneous Dirichlet boundary conditions are considered.

The following stability result is a natural consequence of Theorem 1.

Corollary 1 *Let c and $\tilde{c}$ be solutions of (8)-(11) with initial conditions c_0 and $\tilde{c}_0$, such that $c,\tilde{c}\in L^2(0,T,H^1(-L_v,L_s))$ and $\frac{\partial c}{\partial t},\frac{\partial^2 c}{\partial x^2},\frac{\partial \tilde{c}}{\partial t},\frac{\partial^2 \tilde{c}}{\partial x^2}\in L^2(-L_v,L_s)$, for each $t\in(0,T]$. Then we have*

$$E(t)\leq \|c_0-\tilde{c}_0\|^2+\sum_{i=v,s}D_{1,i}\|\frac{dc_0}{dx}-\frac{d\tilde{c}_0}{dx}\|^2_{L^2(I_i)},\ t\in[0,T].$$

If the variational problem: find $c\in L^2(0,T,H^1(-L_v,L_s))$ such that $\frac{\partial c}{\partial t}\in L^2(-L_v,L_s)$, c satisfies (9)-(11) and the following variational equality

$$(\frac{\partial c}{\partial t}(t),v)+\sum_{i=v,s}\Big(D_{1,i}(\frac{\partial c}{\partial x}(t),\frac{dv}{dx})_{I_i}+\frac{D_{2,i}}{\tau_i}\int_0^t e^{-\frac{t-s}{\tau_i}}(\frac{\partial c}{\partial x}(s),\frac{dv}{dx})_{I_i}\,ds\Big)=0, \tag{17}$$

$\forall v\in H^1(-L_v,L_s)$, has a solution c then, from Theorem 1, c is unique. In fact if we assume that the previous variational problem has two solutions c and $\tilde{c}$ then $w=c-\tilde{c}$ is solution of the same problem with null initial condition. By Theorem 1 for w we have $E(t)=0$, for all $t\geq 0$. Consequently $w=0$ almost every where which implies that $c=\tilde{c}$ in $L^2(-L_v,L_s)$.

3 A discrete model

Our aim in this section is to introduce a discretization of the IBVP (8)-(11) which mimics its continuous counterpart. The discrete model is obtained discretizing the partial derivatives in equation (8) by using cell-centered finite-difference operators and considering for the integral term the rectangular rule.

We define the time grid $\{t_n, n = 0, 1, 2, \dots\}$,

$$t_0 = 0,\ t_{n+1} = t_n + k,\ n = 0, 1, 2, \dots$$

where k is the time-step. In the space domain $[-L_v, L_s]$ we introduce the grid

$$\{x_0 = -L_v, x_i = x_{i-1} + h,\ i = 1, \dots, M, x_M = L_s\},$$

where $h = \dfrac{L_v + L_s}{M}$ and $x_N = 0$ is the transition point. By $x_{i+1/2}$ we represent the center of the cell $[x_i, x_{i+1}]$, $i = 0, \dots, M-1$, I_h and $\bar{I}_h$ denote, respectively, the sets $\{x_{i+1/2}, i = 0, \dots, M-1\}$ and $\bar{I}_h = I_h \cup \{x_0, x_M\}$. Let $I_{h,v} = I_h \cap [-L_v, 0]$ and $I_{h,s} = I_h \cap [0, L_s]$. Let $x_{-1/2}$ and $x_{M+1/2}$ be the auxiliary points $x_{-1/2} = -L_v - \dfrac{h}{2}, x_{M+1/2} = x_M + \dfrac{h}{2}$. For grid functions v_h defined in $\bar{I}_h \cup \{x_{-1/2}, x_{M+1/2}\}$ we introduce the finite-difference formula $\Delta_h v_h(x_{i+1/2})$ defined as the usual second-order finite difference quotient when $i \neq 0, N-1, N, N+1, M-1, M$. $\Delta_h v_h(x_0)$ and $\Delta_h v_h(x_M)$ are defined using a boundary point, a cell-center point and the auxiliary points $x_{-1/2}$ and $x_{M+1/2}$, respectively. If $x_{i+1/2}$ is such that x_i or x_{i+1} is a boundary point or x_N then $\Delta_h v_h(x_{i+1/2})$ is defined by using $x_{i+1/2}$, the boundary point or x_N and neighbor cell-center point.

Let D_{-t} be the backward finite difference operator with respect to the time variable and D_c the first-order centered finite difference quotient defined with respect to the space variable x by the auxiliary point and the cell-center point. D_{-x} and D_x represent, respectively, backward and forward finite difference operators defined using x_N and neighbor cell-center points.

By $c_h^n(x_i)$ we represent the approximation to $c(x_i, t_n)$ defined by the system of equations

$$\begin{aligned} D_{-t}c_h^{n+1}(x_i) &= D_{1,v}\Delta_h c_h^{n+1}(x_i) + k\frac{D_{2,v}}{\tau_v}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_v}} \Delta_h c_h^j(x_i),\ x_i \in I_{h,v} \cup \{x_0\}, \\ D_{-t}c_h^{n+1}(x_i) &= D_{1,s}\Delta_h c_h^{n+1}(x_i) + k\frac{D_{2,s}}{\tau_s}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_s}} \Delta_h c_h^j(x_i),\ x_i \in I_{h,s} \cup \{x_M\}, \end{aligned} \tag{18}$$

with the boundary conditions

$$\begin{aligned} D_{1,v}D_c c_h^{n+1}(x_0) + k\frac{D_{2,v}}{\tau_v}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_v}} D_c c_h^j(x_0) = 0, \\ D_{1,s}D_c c_h^{n+1}(x_M) + k\frac{D_{2,s}}{\tau_s}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_s}} D_c c_h^j(x_M) + r c_h^{n+1}(x_M) = 0, \end{aligned} \tag{19}$$

and the discrete transition condition on x_N

$$\begin{aligned} & D_{1,v}D_{-x}c_h^{n+1}(x_N) + k\frac{D_{2,v}}{\tau_v}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_v}} D_{-x}c_h^j(x_N) \\ &= D_{1,s}D_x c_h^{n+1}(x_N) + k\frac{D_{2,s}}{\tau_s}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_s}} D_x c_h^j(x_N). \end{aligned} \tag{20}$$

The initial values $c_h^0(x_i)$ are given by

$$c_h^0(x_i) = c_0(x_i),\ x_i \in \bar{I}_h. \tag{21}$$

3.1 Stability analysis

In order to study the stability of the numerical methods, let us introduce some notation. We denote by $L^2(\bar{I}_h)$ the space of grid functions v_h defined in $\bar{I}_h$. In this space, we will consider the discrete inner product

$$(v_h, w_h)_h = (v_h, w_h)_v + (v_h, w_h)_s$$

where

$$\begin{aligned}(v_h, w_h)_v = \ & \frac{h}{4} v_h(x_0) w_h(x_0) + \frac{3}{4} h v_h(x_{1/2}) w_h(x_{1/2}) + h \sum_{i=1}^{N-2} v_h(x_{i+1/2}) w_h(x_{i+1/2}) \\ & + \frac{3}{4} h v_h(x_{N-1/2}) w_h(x_{N-1/2}), \\ (v_h, w_h)_s = \ & \frac{3}{4} h v_h(x_{N+1/2}) w_h(x_{N+1/2}) + h \sum_{i=N+1}^{M-2} v_h(x_{i+1/2}) w_h(x_{i+1/2}) \\ & + \frac{3}{4} h v_h(x_{M-1/2}) w_h(x_{M-1/2}) + \frac{h}{4} v_h(x_M) w_h(x_M),\end{aligned}$$

for $v_h, w_h \in L^2(\bar{I}_h)$. We denote by $\|\cdot\|_h$ the norm induced by this inner product. We also need to introduce the following notation

$$(v_h, w_h)_{h+} = (v_h, w_h)_{hv+} + (v_h, w_h)_{hs+}$$

for grid functions defined on $I_h \cup \{x_N, x_M\}$, where

$$\begin{aligned}(v_h, w_h)_{hv+} \ = \ & \frac{h}{2} v_h(x_{1/2}) w_h(x_{1/2}) + h \sum_{i=1}^{N-1} v_h(x_{i+1/2}) w_h(x_{i+1/2}) \\ & + \frac{h}{2} v_h(x_N) w_h(x_N), \\ (v_h, w_h)_{hs+} \ = \ & \frac{h}{2} v_h(x_{N+1/2}) w_h(x_{N+1/2}) + h \sum_{i=N+1}^{M-1} v_h(x_{i+1/2}) w_h(x_{i+1/2}) \\ & + \frac{h}{2} v_h(x_M) w_h(x_M)\end{aligned}$$

and

$$\|v_h\|_{h+}^2 = \|v_h\|_{hv+}^2 + \|v_h\|_{hs+}^2,$$

with

$$\|v_h\|_{hi+}^2 \ = (v_h, v_h)_{hi+},$$

for $i = v, s$.

The following lemma has a central role in the proof of the main stability result of this section and it can be proved using summation by parts.

Lemma 1 *Let w_h, v_h be grid functions defined in $\bar{I}_h \cup \{x_{-1/2}, x_N, x_{M+1/2}\}$. Then*

$$\begin{aligned}(\alpha_v \Delta_h v_h, w_h)_v + (\alpha_s \Delta_h v_h, w_h)_s \ = & -\alpha_v (D_{-x} v_h, D_{-x} w_h)_{hv+} - \alpha_v D_c v_h(x_0) w_h(x_0) \\ & + \alpha_v D_{-x} v_h(x_N) w_h(x_N) - \alpha_s D_x v_h(x_N) w_h(x_N) \\ & - \alpha_s (D_{-x} v_h, D_{-x} w_h)_{hs+} + \alpha_s D_c v_h(x_M) w_h(x_M).\end{aligned}$$

The main stability result is established in the next theorem.

Theorem 2 *Let c_h^n be a solution of the finite-difference problem (18)-(21). Then*

$$\|c_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 \leq \|c_h^0\|_h^2. \tag{22}$$

Proof: Multiplying (18) by c_h^{n+1} with respect to the inner product $(.,.)_h$ and using summation by parts we obtain

$$\begin{aligned}
\|c_h^{n+1}\|_h^2 &= (c_h^n, c_h^{n+1})_h - k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 \\
&-k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}}(D_{-x}c_h^j, D_{-x}c_h^{n+1})_{hi+} \\
&-kc_h^{n+1}(x_0)\Big(D_{1,v}D_c c_h^{n+1}(x_0) + \frac{D_{2,v}}{\tau_v}k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_v}} D_c c_h^j(x_0)\Big) \\
&+kc_h^{n+1}(x_N)\Big(D_{1,v}D_{-x}c_h^{n+1}(x_N) + \frac{D_{2,v}}{\tau_v}k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_v}} D_{-x}c_h^j(x_N)\Big) \\
&-kc_h^{n+1}(x_N)\Big(D_{1,s}D_x c_h^{n+1}(x_N) + \frac{D_{2,s}}{\tau_s}k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_s}} D_x c_h^j(x_N)\Big) \\
&+kc_h^{n+1}(x_M)\Big(D_{1,s}D_c c_h^{n+1}(x_M) + \frac{D_{2,s}}{\tau_s}k\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_s}} D_c c_h^j(x_M)\Big).
\end{aligned} \tag{23}$$

Taking the boundary conditions (19) and the transition condition (20) into account in (23) we deduce that

$$\begin{aligned}
\|c_h^{n+1}\|_h^2 &= (c_h^n, c_h^{n+1})_h - k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 \\
&-k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}}(D_{-x}c_h^j, D_{-x}c_h^{n+1})_{hi+} - rc_h^{n+1}(x_M)^2.
\end{aligned} \tag{24}$$

As we have

$$\begin{aligned}
(\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}c_h^j, D_{-x}c_h^{n+1})_{hi+} &= \frac{1}{2}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 \\
&-\frac{e^{-2\frac{k}{\tau_i}}}{2}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 + \frac{1}{2}\|D_{-x}c_h^{n+1}\|_{hi+}^2,
\end{aligned}$$

using the Cauchy-Schwarz inequality, from (24) we obtain

$$\begin{aligned}
&\frac{1}{2}\|c_h^{n+1}\|_h^2 + \frac{k}{2}\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 + \frac{k^2}{2}\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 \\
&\leq \frac{1}{2}\|c_h^n\|_h^2 - \frac{k}{2}\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 + \frac{k^2}{2}\sum_{i=v,s} e^{-\frac{2k}{\tau_i}}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 \\
&-\frac{k^2}{2}\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|D_{-x}c_h^{n+1}\|_{hi+}^2,
\end{aligned}$$

which leads to

$$\begin{aligned}
&\|c_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 \\
&\leq \|c_h^n\|_h^2 - k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s} e^{-\frac{2k}{\tau_i}}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2.
\end{aligned} \tag{25}$$

Inequality (25) holds for $n \geq 1$ and we get

$$\begin{aligned}
&\|c_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}c_h^j\|_{hi+}^2 \\
&\qquad\leq \|c_h^1\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^1\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|D_{-x}c_h^1\|_{hi+}^2.
\end{aligned} \tag{26}$$

Following the proof of inequality (25) and considering (18) with $n = 0$, it can be shown that

$$\|c_h^1\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}c_h^1\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|D_{-x}c_h^1\|_{hi+}^2 \leq \|c_h^0\|_h^2. \tag{27}$$

From (26) and (27) we conclude (22).

■

The following corollaries are consequence of Theorem 2.

Corollary 2 *The finite difference scheme (18)-(21) has at most one solution.*

Corollary 3 *If $c_h^n, \tilde{c}_h^n$ are solutions of the finite difference problem (18)-(21) with the same boundary conditions and with the initial conditions c_h^0 and $\tilde{c}_h^0$, respectively, then $w_h^n = c_h^n - \tilde{c}_h^n$ satisfies*

$$\begin{aligned}
&\|w_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}w_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}w_h^j\|_{hi+}^2 \\
&\leq \|c_h^0 - \tilde{c}_h^0\|_h^2.
\end{aligned}$$

3.2 Convergence

Let $e_h^n(x_i) = c(x_i,t_n) - c_h^n(x_i)$ be the global error and let $T_h^n(x_i)$ be the correspondent truncation error at $x_i \in \bar{I}_h$. We denote by $T_{h,v}^n$, $T_{h,s}^n$ and $T_{h,t}^n$ the truncation errors in $I_{h,v}\cup\{x_0\}$, $I_{h,s}\cup\{x_M\}$ and $\{x_N\}$, respectively. These errors are related by the following finite-difference equations

$$D_{-t}e_h^{n+1}(x_i) = D_{1,v}\Delta_h e_h^{n+1}(x_i) + k\frac{D_{2,v}}{\tau_v}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_v}}\Delta_h e_h^j(x_i) + T_{h,v}^{n+1}(x_i),$$

$x_i \in I_{h,v}\cup\{x_0\}$,

$$D_{-t}e_h^{n+1}(x_i) = D_{1,s}\Delta_h e_h^{n+1}(x_i) + k\frac{D_{2,s}}{\tau_s}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_s}}\Delta_h e_h^j(x_i) + T_{h,s}^{n+1}(x_i),$$

$x_i \in I_{h,s} \cup \{x_M\}$, with the boundary conditions

$$D_{1,v} D_c e_h^{n+1}(x_0) + k\frac{D_{2,v}}{\tau_v}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_v}} D_c e_h^j(x_0) = T_{h,v}^n(x_0),$$

$$D_{1,s} D_c e_h^{n+1}(x_M) + k\frac{D_{2,s}}{\tau_s}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_s}} D_c e_h^j(x_M) + r e_h^{n+1}(x_M) = T_{h,s}^{n+1}(x_M),$$

and the discrete transition condition on x_N

$$D_{1,v} D_{-x} e_h^{n+1}(x_N) + k\frac{D_{2,v}}{\tau_v}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_v}} D_{-x} e_h^j(x_N)$$
$$= D_{1,s} D_x e_h^{n+1}(x_N) + k\frac{D_{2,s}}{\tau_s}\sum_{j=1}^{n+1} e^{\frac{t_{n+1}-t_j}{\tau_s}} D_x e_h^j(x_N) + T_{h,t}^{n+1}(x_N).$$

The initial values $e_h^0(x_i)$ are given by

$$e_h^0(x_i) = 0,\ x_i \in \overline{I}_h.$$

Theorem 3 *Let c_h^n be defined by (18)-(21) and let c be the solution of (8)-(11). The error e_h^n satisfies the following inequality*

$$\begin{aligned} &\|e_h^n\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^n\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\ &\leq e^{\frac{8\eta^2(n-1)k}{1-8\eta^2 k}}\frac{1+8\eta^2 k}{8\eta^2(1-8\eta^2 k)}\max_{i=1,\ldots,n}\mathcal{T}_h^i, \end{aligned} \tag{28}$$

where η denotes a non zero constant provided that

$$1 - 8\eta^2 k > 0, \tag{29}$$

and $\mathcal{T}_h^j$ is defined by

$$\mathcal{T}_h^j = \frac{1}{2\eta^2}\Big(\|T_h^j\|_h^2 + \frac{1}{h}\big((T_{h,v}^j(x_0))^2 + (T_{h,s}^j(x_M))^2\big) + \frac{2}{h}(T_{h,t}^j(x_N))^2\Big) + \frac{L_v}{2\epsilon^2}(T_{h,t}^j(x_N))^2.$$

where ϵ is such that

$$\epsilon^2 - \frac{D_{1,v}}{2} \leq 0. \tag{30}$$

Proof: Following the proof of Theorem 2 it can be shown that for e_h^n we have

$$\begin{aligned} &\|e_h^{n+1}\|_h^2 + \frac{k}{2}\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^{n+1}\|_{hi+}^2 + \frac{k^2}{2}\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\ &\leq (e_h^n, e_h^{n+1}) - \frac{k}{2}\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^{n+1}\|_{hi+}^2 + \frac{k^2}{2}\sum_{i=v,s} e^{-\frac{2k}{\tau_i}}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\ &-\frac{k^2}{2}\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|D_{-x}e_h^{n+1}\|_{hi+}^2 + k(T_h^{n+1}, e_h^{n+1}) - k e_h^{n+1}(x_0) T_{h,v}^{n+1}(x_0) \\ &-k e_h^{n+1}(x_N) T_{h,t}^{n+1}(x_N) + k e_h^{n+1}(x_M)\big(-r e_h^{n+1}(x_M) + T_{h,s}^{n+1}(x_M)\big). \end{aligned} \tag{31}$$

Using the following representation

$$\begin{aligned} e_h^{n+1}(x_N) &= e_h^{n+1}(x_0) + \frac{h}{2}\frac{e_h^{n+1}(x_{1/2}) - e_h^{n+1}(x_0)}{h/2} + \sum_{i=1}^{N-1} hD_{-x}e_h^{n+1}(x_{i+1/2}) \\ &+ \frac{h}{2}\frac{e_h^{n+1}(x_N) - e_h^{n+1}(x_{N-1/2})}{h/2} \end{aligned}$$

it can be shown that

$$-e_h^{n+1}(x_N)T_{h,t}^{n+1}(x_N) \le \epsilon^2 \|D_{-x}e_h^{n+1}\|_{hv+}^2 + \eta^2\|e_h^{n+1}\|_h^2 + (T_{h,t}^{n+1}(x_N))^2(\frac{1}{\eta^2 h} + \frac{L_v}{4\epsilon^2}), \tag{32}$$

where η and ϵ are arbitrary non zero constants.

Considering (31), (32) and the inequalities

$$\begin{aligned} e_h^{n+1}(x_0)T_{h,v}^n(x_0) + e_h^{n+1}(x_M)T_{h,s}^n(x_M) &\le 2\eta^2\|e_h^{n+1}\|^2 + \frac{1}{4\eta^2 h}\big((T_{h,v}^{n+1}(x_0))^2 \\ &\quad +(T_{h,s}^{n+1}(x_M))^2\big), \end{aligned}$$

$$(e_h^n, e_h^{n+1}) \le \frac{1}{2}\|e_h^n\|^2 + \frac{1}{2}\|e_n^{n+1}\|^2,$$

$$(T_h^{n+1}, e_h^{n+1}) \le \eta^2\|e_h^{n+1}\|^2 + \frac{1}{4\eta^2}\|T_h^{n+1}\|^2,$$

we obtain

$$\begin{aligned} &(1-8\eta^2 k)\|e_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^{n+1}\|_{hi+}^2 \\ &+k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\ &\le \|e_h^n\|^2 + 2k(\epsilon^2 - \frac{D_{1,v}}{2})\|D_{-x}e_h^{n+1}\|_{hv+}^2 - kD_{1,s}\|D_{-x}e_h^{n+1}\|_{hs+}^2 \\ &+k^2\sum_{i=v,s} e^{-\frac{2k}{\tau_i}}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\ &+k\Big(\frac{1}{2\eta^2}\big(\|T_h^{n+1}\|_h^2 + \frac{1}{h}\big((T_{h,v}^{n+1}(x_0))^2 + (T_{h,s}^{n+1}(x_M))^2\big) + \frac{2}{h}(T_{h,t}^{n+1}(x_N))^2\big) \\ &+\frac{L_v}{2\epsilon^2}(T_{h,t}^{n+1}(x_N))^2\Big). \end{aligned} \tag{33}$$

If ϵ is fixed and satisfies (30) then, from (33), we obtain

$$\begin{aligned} &\|e_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\ &\le \frac{1}{1-8\eta^2 k}\Big(\|e_h^n\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^n\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2\Big) \\ &+\frac{k}{1-8\eta^2 k}\mathcal{T}_h^{n+1}, \end{aligned} \tag{34}$$

provided that k satisfies (29).

The inequality (34) implies that, for $n \geq 2$,

$$\begin{aligned}
&\|e_h^n\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^n\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\
&\leq \Big(\frac{1}{1-8\eta^2 k}\Big)^{n-1}\Big(\|e_h^1\|_h^2 + k\sum_{i=v,s}\Big(D_{1,i} + k\frac{D_{2,i}}{\tau_i}\Big)\|D_{-x}e_h^1\|_{hi+}^2 + \frac{1}{8\eta^2}\max_{i=2,\ldots,n}\mathcal{T}_h^i\Big).
\end{aligned} \tag{35}$$

As for e_h^1 it can be shown that the following estimate holds

$$\|e_h^1\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^1\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|D_{-x}e_h^j\|_{hi+}^2 \leq \frac{k}{1-8\eta^2 k}\mathcal{T}_h^1,$$

from (35) we deduce

$$\begin{aligned}
&\|e_h^n\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^n\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\
&\leq \Big(\frac{1}{1-8\eta^2 k}\Big)^{n-1}\frac{1+8\eta^2 k}{8\eta^2(1-8\eta^2 k)}\max_{i=1,\ldots,n}\mathcal{T}_h^i\Big),
\end{aligned}$$

which concludes the proof of (28). ■

We remark that if c, as a function of x, belongs to $C^{3,1}[-L_v, L_s] - \{0\}$, then $T_h(x_N) = O(h)$ and consequently $\mathcal{T}_h^i = O(h)$ leading to

$$\|e_h^n\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^n\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 = O(h) + O(k^2).$$

If the concentration is known for all time t at $x = -L_v$, that is, if we assume a Dirichlet boundary condition at $x = -L_v$, then $e_h^{n+1}(x_0) = 0$. In what concerns the term $e_h^{n+1}(x_M)$ of (31) we can prove that

$$e_h^{n+1}(x_M)T_{h,s}^{n+1}(x_M) \leq \sum_{i=v,s}\gamma_i^2\|D_{-x}e_h^{n+1}\|_{hi+}^2 + T_{h,s}^{n+1}(x_M)^2\sum_{i=v,s}\frac{L_i}{4\gamma_i},$$

where γ_i, $i = v, s$, denote positive constants. Then (33) is replaced by

$$\begin{aligned}
&(1-4\eta^2 k)\|e_h^{n+1}\|_h^2 + k\sum_{i=v,s} D_{1,i}\|D_{-x}e_h^{n+1}\|_{hi+}^2 + k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\
&\leq \|e_h^n\|_h^2 + 2k(\epsilon^2 + \gamma_v^2 - \frac{D_{1,v}}{2})\|D_{-x}e_h^{n+1}\|_{hv+}^2 + 2k(\gamma_s^2 - \frac{D_{1,s}}{2})\|D_{-x}e_h^{n+1}\|_{hs+}^2 \\
&+k^2\sum_{i=v,s}\frac{D_{2,i}}{\tau_i}\|\sum_{j=1}^{n} e^{-\frac{t_n-t_j}{\tau_i}} D_{-x}e_h^j\|_{hi+}^2 \\
&+k\Big(\|T_h^{n+1}\|_h^2 + \frac{L_v}{2\epsilon^2}(T_{h,t}^{n+1}(x_N))^2 + T_h^{n+1}(x_M)\frac{1}{2}(\frac{L_v}{\gamma_v^2} + \frac{L_s}{\gamma_s^2})\Big).
\end{aligned}$$

Let γ_i, $i = v, s$ and ϵ be such that

$$\epsilon^2 + \gamma_v^2 - \frac{D_{1,v}}{2} \leq 0,\ \gamma_s^2 - \frac{D_{1,s}}{2} \leq 0.$$

Then, for k satisfying

$$1 - 4\eta^2 k > 0,$$

we obtain

$$\begin{aligned}
&\|e_h^{n+1}\|_h^2 + k \sum_{i=v,s} D_{1,i} \|D_{-x} e_h^{n+1}\|_{hi+}^2 + k^2 \sum_{i=v,s} \frac{D_{2,i}}{\tau_i} \|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x} e_h^j\|_{hi+}^2 \\
&\leq \frac{1}{1-4\eta^2 k} \|e_h^n\|_h^2 + k \sum_{i=v,s} D_{1,i} \|D_{-x} e_h^{n+1}\|_{hi+}^2 \\
&+ k^2 \sum_{i=v,s} \frac{D_{2,i}}{\tau_i} \|\sum_{j=1}^{n} e^{-\frac{t_n - t_j}{\tau_i}} D_{-x} e_h^j\|_{hi+}^2 \\
&+ \frac{k}{1-4\eta^2 k}\Big(\|T_h^{n+1}\|_h^2 + \frac{L_v}{2\epsilon^2}(T_{h,t}^{n+1}(x_N))^2 + T_h^{n+1}(x_M)\frac{1}{2}\big(\frac{L_v}{\gamma_v^2} + \frac{L_s}{\gamma_s^2}\big)\Big).
\end{aligned}$$

Following the proof of Theorem 3, it can be shown that

$$\begin{aligned}
&\|e_h^{n+1}\|_h^2 + k \textstyle\sum_{i=v,s} D_{1,i} \|D_{-x} e_h^{n+1}\|_{hi+}^2 + k^2 \sum_{i=v,s} \frac{D_{2,i}}{\tau_i} \|\sum_{j=1}^{n+1} e^{-\frac{t_{n+1}-t_j}{\tau_i}} D_{-x} e_h^j\|_{hi+}^2 \\
&= O(k^2) + O(h^4) + O(h^2),
\end{aligned}$$

where the term $O(h^2)$ is associated with $\dfrac{L_v}{2\epsilon^2}(T_{h,t}^{n+1}(x_N))^2$.

4 Numerical results

We first compare numerically the behaviour of the proposed model with the diffusion model considered for instance in [20] and [28], which is defined by the diffusion equations (1), the initial condition (5), the boundary conditions (2), (3) and the transition condition (4). The discretization of the the diffusion equations are obtained using the same numerical method we used for the integro-differential model, with $D_{2,i} = 0, i = v, s$.

For the simulation we consider that initially there is no drug in the skin and the concentration in the vehicle is 1, i.e.,

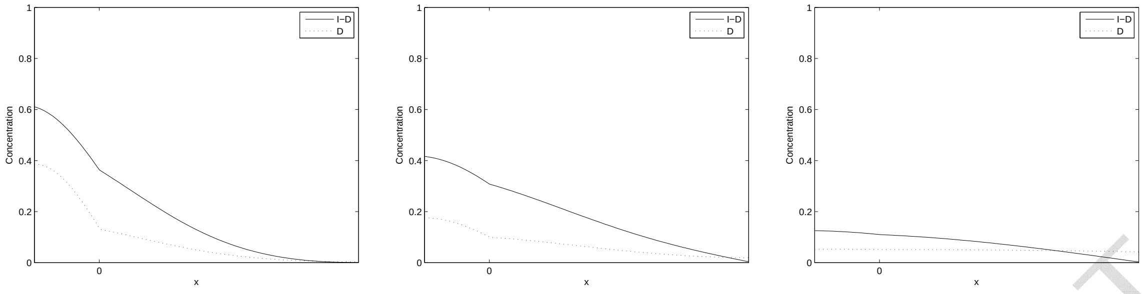
$$c(x, 0) = 1,\ -L_v < x \leq 0, \quad c(x, 0) = 0,\ 0 < x < L_s.$$

In all numerical experiments, we use the following constant values: $L_v = 0.2$, $L_s = 0.8$, $D_v = 0.5$ and $D_s = 1$. For the boundary condition we consider $r = 0.5$.

In the first example we took the parameters $D_{1,v} = 0.05$, $D_{2,v} = 0.45$, $D_{1,s} = 0.1$ and $D_{2,s} = 0.9$, for the integro-differential model. The results are plotted in Figure 2.

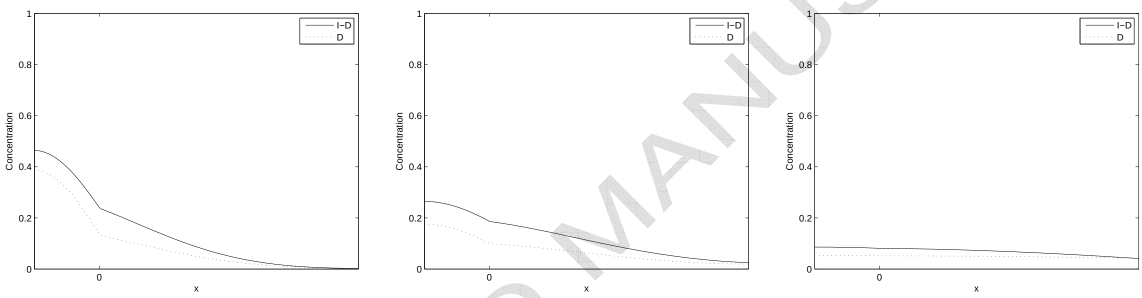
The results considering $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$ and $D_{2,s} = 0.5$ are plotted in Figure 3.

As we expected, in both examples, the propagation velocity of the numerical approximations to the solution of the integro-differential model is lower.



$T = 0.05$ $T = 0.1$ $T = 0.5$

Figure 2: Concentration using the differential model (D) and the integro-differential model (I-D), $D_{1,v} = 0.05$, $D_{2,v} = 0.45$, $D_{1,s} = 0.1$, $D_{2,s} = 0.9$, $\tau_v = 0.005$, $\tau_s = 0.005$, with $k = 0.00001$ and $h = 0.0125$.



$T = 0.05$ $T = 0.1$ $T = 0.5$

Figure 3: Concentration using the differential model (D) and the integro-differential model (I-D), $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$, $D_{2,s} = 0.5$, $\tau_v = 0.005$, $\tau_s = 0.005$, $k = 0.00001$ and $h = 0.0125$.

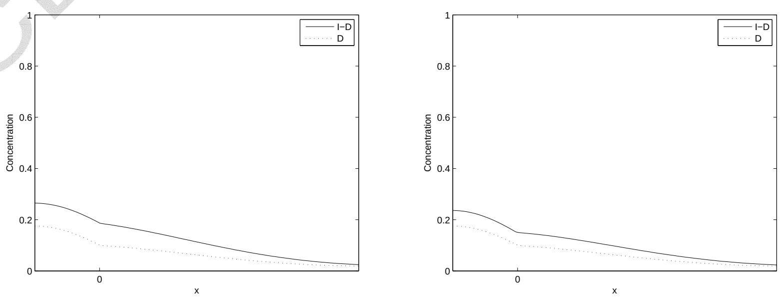


Figure 4: Concentration using the differential model (D) and the integro-differential model (I-D), $\tau_v = 0.005$, $\tau_s = 0.005$ (left), $\tau_v = 0.00005$, $\tau_s = 0.00005$ (right) with $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$, $D_{2,s} = 0.5$, $k = 0.0001$, $h = 0.0001$ and $T = 0.1$.

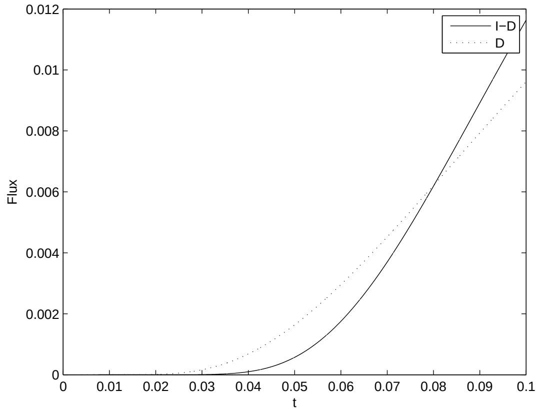


Figure 5: Time *versus* flux at the point $x = L_s$, $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$, $D_{2,s} = 0.5$, $\tau_v = 0.005$, $\tau_s = 0.005$, $k = 0.00001$ and $h = 0.0125$.

In Figure 4 the values of τ_v and τ_s change. We observe that for smaller values the two curves are closer.

Figure 5 shows the flux along the time at the extreme point $x = L_s$.

In Tables 1 and 2, the rate of convergence is computed using the numerical solutions corresponding to mesh-sizes h and $h/2$. The error is defined by the right hand side of (28). The error is computed using a numerical solution obtained with a much finer mesh, taking $h = 9.766e-05$ and $k = 1.000e-08$, since the exact solution is not available. In Table 1 we consider $T = 0.01$ and, in Table 2, $T = 0.1$.

h	N_v	N_s	$error$	rate
1.000e-01	2	8	7.896e-04	2.66
5.000e-02	4	16	1.247e-04	1.72
2.500e-02	8	32	3.790e-05	1.93
1.250e-02	16	64	9.969e-06	2.01
6.250e-03	32	128	2.483e-06	2.03
3.125e-03	64	256	6.064e-07	2.07
1.563e-03	128	512	1.446e-07	-

Table 1: Rate of convergence, $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$, $D_{2,s} = 0.5$, $\tau_v = 0.01$, $\tau_s = 0.01$, $k = 1e-08$, $T = 0.01$.

Table 3 shows the variation of the rate of convergence with k.

Theorem 3 establishes that the convergence order is equal to one with respect to the time step size and $\dfrac{1}{2}$ with respect to space step size. The numerical estimates for the rate of convergence presented in Tables 1,2 are bigger than the rate of convergence, with respect to the space step size, theoretically established in Theorem 3. From Table 3, we conclude that the numerical estimates confirm the theoretical estimate given in the previous result for the rate of convergence with respect to the time step size.

h	N_v	N_s	$error$	rate
1.000e-01	2	8	6.493e-04	1.99
5.000e-02	4	16	1.629e-04	2.02
2.500e-02	8	32	4.023e-05	1.99
1.250e-02	1.6	64	1.011e-05	1.95
6.250e-03	32	128	2.618e-06	1.88
3.125e-03	64	256	7.122e-07	1.76
1.563e-03	128	512	2.101e-07	-

Table 2: Rate of convergence, $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$, $D_{2,s} = 0.5$, $\tau_v = 0.01$, $\tau_s = 0.01$, $k = 1e-08$, $T = 0.1$.

k	$error$	rate
1.000e-04	3.909e-04	1.82
5.000e-05	1.104e-04	1.91
2.500e-05	2.938e-05	1.95
1.250e-05	7.580e-06	1.98
6.250e-06	1.923e-06	1.99
3.125e-06	4.831e-07	2.00
1.563e-06	1.205e-07	-

Table 3: Rate of convergence, $D_{1,v} = 0.25$, $D_{2,v} = 0.25$, $D_{1,s} = 0.5$, $D_{2,s} = 0.5$, $\tau_v = 0.01$, $\tau_s = 0.01$, $h = 6.250e-03$, $T = 0.1$.

5 Conclusions

The coupled vehicle-skin system is usually modeled by using the classical diffusion equation. The numerical results obtained from such a model lead to concentration profiles which do not agree with experimental data. In fact experimental data profiles present a delay effect. In order to introduce the delay effect in the diffusion phenomenon an integro-differential model was introduced in this paper.

The integro-differential model is established replacing Fick's law for the flux by a new law where a delay parameter τ is introduced. Of course when $\tau \to 0$, the new law for the flux coincides with Fick's law and consequently the new model coincides with the classical diffusion model.

The stability of the integro-differential model was established as a consequence of energy estimates. These estimates enable us to characterize the qualitative behaviour of the drug concentration in space and in time.

Numerical methods for drug concentrations were introduced and their stability properties were established. The approximations obtained with these methods have the same qualitative properties of the drug concentrations defined by the integro-differential model. In fact the results proved for the discrete case can be seen as discretizations of the continuous counterpart. The numerical experiments illustrate the delay effect of the new model.

The convergence properties of the numerical methods were analyzed and the numerical results illustrate the proved convergence results.

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